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EDITORIAL

The Future of Endovascular Aneurysm Repair

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Over the past 10 years, there has been a rapid development in techniques for the endovascular repair of abdominal aortic aneurysms (EVAR). A mixed picture is emerging from the growing evidence-base, which includes recent publications of the medium term results of large registries,[1,2] the first reports of randomised controlled trials (RCTs)[3,4] and a systematic literature review that includes nearly 20,000 reported cases of EVAR.[5]

The investigation of new technologies and interpretation of early published evidence raise a number of difficulties. Early results may suffer from publication bias tending to emphasise positive outcomes and, due to the desire for rapid publication, concentrating on short-term results. Early technology is unstable and continues to evolve, with many prototype devices being superceded by the time that results are published. Those carrying out the procedures may have a steep learning curve and the relevant population for the procedure may not have been clearly defined, leading to a lack of comparable case-mix in early-published series. There are also specific issues around the comparison of procedures where one is far less invasive than another, making it difficult to recruit patients to randomised controlled trials or causing confounding through high rates of crossover between the arms of the trial.

Finally, there are conflicting pressures from consumers keen to adopt new and minimally invasive techniques, healthcare providers who wish to ensure value for money and commercial concerns, keen to get an early return on the considerable investment that is required in the new technology.

Given these difficulties it is heartening to see recent major publications from the two UK EVAR trials, providing high quality medium term data relating to the procedure, and the organisers of these studies are to be congratulated on a considerable achievement. The two trials consider different clinical circumstances with EVAR 1 comparing the procedure with open repair in a fit population[6] and EVAR 2 comparing it with best medical management in those considered unfit for surgery.[7]

So where do we currently stand with regard to the evidence on EVAR, and how might we move forward?

As might be expected, there are clear early benefits with lower procedure-related mortality following EVAR. The initial results of the EVAR 1 trial reported a significant reduction in 30-day mortality from 4.7% for open repair to 1.7% for EVAR,[3] and this was consistent with the mortality benefit seen in the DREAM trial[4] and with the collected non-randomised comparisons in the systematic review.[5] Meta-analysis from the review suggests a significant benefit, with an odds ratio of 0.33 (CI 0.26–0.42) for 30-day mortality following EVAR as compared with open surgical repair. The evidence that EVAR has a mortality that is about a third of that seen following conventional repair is enough to boost demand for the procedure, but may lead to future difficulties in randomising a population that is being offered an invasive treatment for a condition that is usually asymptomatic.

In those who are unfit for surgical repair the registries suggest a much higher initial procedure-related mortality and the RCT evidence of the EVAR 2 trial estimates the 30-day mortality to be 9%, which is in keeping with the subgroup analysis from the RETA registry.[1] Although this figure may seem relatively high it is within the range of reported mortality following open repair[8] and may be justified in a population with a significant risk of death from aneurysm rupture.

However, the procedure is a prophylactic one with the benefit depending upon how well it protects against the risks of untreated aneurysm, and this is

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where the evidence is less clear. Medium term results from the randomised controlled trials have failed to show overall survival advantages and all the evidence demonstrates a significant rate of endoleak and late aneurysm expansion, with the need for continuing surveillance and re-intervention. The EVAR 1 trial showed a rate of re-intervention of 6.9 per 100 patient years following EVAR compared with 2.4 following open repair and overall complication rates were 17.6 *vs*. 3.3 per 100 patient years. The trial results suggest that the higher complication rate and increased need for re-intervention persist in the medium term and are not restricted to the early period following the procedure. One can argue about whether this is a teething problem of the new technology that will be eliminated as new generations of device are developed or whether it is a fundamental limitation of the current fixation techniques that will require changes to the way that devices are introduced or held in place. However, with consistent results seen in the recently published two-year results of the Dutch Randomised Endovascular Aneurysm Management (DREAM) trial[9] and other large non-randomised series, this is the best current estimate of the likely re-intervention rate.

It might be expected that those patients with co-morbidities that preclude surgical treatment would be most likely to benefit from EVAR; however, this has not been confirmed by the EVAR 2 trial. The high expected aneurysm related mortality did not occur in the non-operative arm of the trial and only 23 aneurysm related deaths were reported, a rate of nine deaths per 100 patient years, approximately matching the procedure-related mortality. With a high total mortality of 64% at 4 years there was no overall survival benefit in the EVAR group. There may be many reasons for this difference between expected and observed aneurysm related mortality. Perhaps the most important is the possibility of an element of confounding due to crossover of patients on best medical management to exclusion by EVAR or surgery. Within the trial these patients would have been under close surveillance and over twice as many patients (47) underwent late aneurysm repair as died of aneurysm related causes. Many of these had enlarging aneurysms or had developed symptoms and may have considerably increased the aneurysm related mortality had such crossovers not occurred.

It is a necessary drawback of RCTs that data needs to be aggregated to produce adequate sample size, whilst in clinical practice estimates of risks and benefits form a continuum. There are four key parameters that are likely to determine the overall balance of risks and benefits in an individual patient with an aneurysm.

Firstly, there is the risk related to the procedure itself, which may be partly predicted from physiological scoring[10] but may also depend on factors specific to the procedure in question, for example the presence of a hostile abdomen for open repair or difficulty in access due to iliac tortuosity for EVAR. Secondly, there is the estimated long-term survival, which may be predicted from factors such as age and the presence of known co-morbidity. The third element is the risk of aneurysm related death if the aneurysm remains untreated. This can largely be predicted from aneurysm size but there remains a question, raised by the EVAR 2 trial, as to the extent to which high-risk patients can be identified by further surveillance and managed by delayed intervention. Finally, we need to understand the factors that predict long term success following EVAR and it is in this area that we have the least information. It may well be that with further experience we will be able to identify factors relating to patient characteristics, aneurysm morphology and technical issues that can help to predict the occurrence of complications and need for further intervention.

Thus, for an individual patient the consideration of specific risk factors may suggest that the general messages of the RCTs are not directly applicable, and yet it would clearly be impossible to carry out further RCTs covering every possible combination of clinical situations. Treatment decisions need to make the best use existing evidence without unjustified extrapolation and generalisation.

Some clear messages emerge from consideration of the current evidence. The first is that although EVAR has significant benefits in terms of early mortality this is offset by an increased need for surveillance and re-intervention and there remains considerable uncertainty about any long-term benefits in overall mortality. For this reason it should still be considered an experimental procedure and informed consent must ensure that patients understand all the limitations and uncertainties, as well as the early benefits.

The second message relates to the nature of further investigation that is required. Whilst it is difficult to reliably assess the potential cost-effectiveness of new techniques at such an early stage, the EVAR trials suggest that there is an excess cost of about £3300 per patient compared to open repair and £8600 compared to non-operative treatment. The latter may well be a considerable underestimate of the true cost due to the high crossover rate within the trial. Economic modelling based on the best evidence that is currently available[11] suggests that for the procedure to be cost-effective would require a significant reduction in the

rate of re-intervention. Thus the key focus for further research needs to be the identification of developments in devices, operator skills and aspects of patient selection that will make it possible to minimise the rate of late complications and the need for re-intervention.

In this respect there are already potential technical advances such as supra-renal fixation, combined laparoscopic and endovascular approaches and the use of fenestrated grafts that have not been assessed in the existing trials. Technology is developing rapidly and one can envisage many further developments over the next few years in areas such as graft materials, fixation techniques, endovascular suturing devices, sealants, introduction methods and monitoring, which may all have potential to reduce the risk of endoleak, migration or other complications.

There are clearly more unanswered than answered questions and the continued scientific evaluation of EVAR will provide many challenges and require a range of scientific approaches. Whilst randomised controlled trials remain the 'gold standard' it is possible that with the dissemination of the evidence of early survival benefits it will become increasingly difficult to randomise patients in further trials. Even where such trials are feasible, the considerable delays inherent in planning, funding and undertaking them may make it difficult to keep up with a rapidly moving field of technology. Alternative trial designs, such as 'tracker trials'[12] may have the flexibility to allow for developing technology and shifting areas of equipoise. However, in practice, it is likely that the vast majority of procedures will occur outside such trials.

Registries have provided a rich source of evidence that has helped to inform device development and assisted with early planning of RCTs. Continuation of the collection of such data is likely to provide the most effective way of monitoring progress in the development of devices and techniques, and in identifying sub-groups and situations in which further RCTs are appropriate. However, given the voluntary nature of previous registries, the need for accurate long-term data and the resources required to maintain and validate these, there must be concerns that these will fail to provide adequate data without some form of compulsion or incentive to participate. In some countries there is the potential for a regulatory body to place conditions on the use of new procedures, and when the procedure was considered in 2003 by the National Institute for Health and Clinical Excellence in the UK it recommended that EVAR was only carried out with as part of clinical trials or with appropriate data submission to a registry.[13] It will be interesting to see the conclusion when they reconsider the procedure in the light of the EVAR trial results.

Finally, there is the issue of how best to use existing and emerging evidence to inform clinical and managerial decision making. The patient with high risk for surgery due to a hostile abdomen presents very different issues from those with severe cardio-respiratory disease or advanced malignancy. Whilst RCT data may be difficult to extrapolate to individual situations, decision-making can be supported by predictive modelling using data from a variety of sources, such as registries and RCT sub-group analysis. With increasing demand for minimally invasive treatment it is likely that EVAR is here to stay. All clinicians undertaking the procedure have a duty to ensure that individual patients can participate in informed decision-making using the most applicable estimates of the risks and benefits, and that future patients can benefit from the continued collection of high quality data to supplement the available information.

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